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REMARKS

Upon entry of the amendment, claims 66-75 will be pending. Claim 72 is rejected under 35 USC 112, paragraph 2 for allegedly being indefinite. Claims 66-75 are variously rejected under 35 USC 102 for allegedly being anticipated by three patent references. The claims have been amended as set forth above. The Applicants submit that in view of the forgoing amendments and the following remarks, the application is now in proper form for allowance.

I. Rejection under 35 USC 112, paragraph 2

Claim 72 is rejected under 35 USC 112, paragraph 2 for allegedly being indefinite for allegedly failing to particularly point out and distinctly claim the subject matter. The Examiner has stated that the claims were examined to be drawn to an oligonucleotide in the various media, rather than being the media. The amendment as set forth above corrects these typographical errors, making the claims clear and definite. These amendments are made for the purpose of clarity and do not alter the scope of the claims.

II. Rejections for anticipation under 102

Claims 66, 72-74 and 76 are rejected under 35 USC 102(b) for allegedly being anticipated by Kole (USP 5,627,274). Claims 66-68 and 70-77 are rejected under 35 USC 102(a) or (e) for being anticipated by Baracchini (USP 5,801,154). Claims 66-77 are rejected under 35 USC 102(a) or (e) for being anticipated by Bennett (USP 5,955,443).

The Examiner states that Kole teaches a method for administering an aerosolized formulation of repirable particles to the lungs, in various formulations, with modified oligonucleotides. Claim 66 has been amended to recite that the particle size is about 1 to about 5 microns. Support for this range is found in Example 2, and demonstration that the particles produced by the nebulizer in the instant application were within that range is provided in Example 3. The in vivo data in Example 3 demonstrate that particles produced by the nebulizer were delivered to at least one cell type in the lung as claimed. Kole provides no teaching regarding particle size for delivery to the lung. Most of the Examples provided teach modulation

of splicing in a HeLa cell extract. This cannot address the issue of cell uptake as the assays are not performed in cells. Example 9 teaches incubation of tissue culture cells with oligonucleotide at a level that "represents 100 fold excess over that required to elicit efficient restoration of splicing in vitro." (col 13, ln 8-10). Such conditions are not relevant to delivery of oligonucleotides to lungs in vivo. Therefore, claims 66, 72-74 and 76 are novel, and not anticipated by Kole.

The Examiner states that Baracchini teaches delivery of antisense oligonucleotides via inhalation or insufflation, in formulations as claimed, with modifications as claimed. The Examiner makes similar statements regarding Bennett. The Applicants submit that in view of the amendment of claim 66, it is neither obvious nor anticipated by the teachings of Baracchini or Bennett.

In column 4, Baracchini provides a list of possible routes of delivery of oligonucleotides. Baracchini does not teach delivery to at least one cell type in the lung. Baracchini teaches effective oligonucleotide delivery in vitro (i.e., in tissue culture) and in vivo by intraperitoneal injection only (Example 6, see specifically col. 18, ln 33-36). There are no teachings regarding selection of particle size for the delivery of oligonucleotide to at least one type of lung cell via inhalation. Therefore, claims 66-68 and 70-77 are novel, and not anticipated by Baracchini.

Bennett provides general teachings similar to Baracchini. Bennett teaches effective oligonucleotide delivery in vitro (i.e., in tissue culture) and in vivo by intravenous injection (Example 8, see specifically col. 54, ln 40-42). There are no teachings regarding selection of particle size for the delivery of oligonucleotide to at least one type of lung cell by inhalation. Therefore, claims 66-77 are are novel, and not anticipated by Bennett.

III. Consideration of Supplemental Information Disclosure Statements

Supplemental Information Disclosure Statements were filed by Applicants on August 22, 2003 and December 15, 2004. Applicants are not in receipt of initialed copies of the documents and they could not be found on PAIR. Applicants again request that the Examiner consider the references cited and forward a copy of the initialed documents to Applicants.

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FEES

The Applicants hereby authorize to Commissioner to charge Deposit Account 50-0252 referencing case number ISIS-3561 the fee for a Request for Continued Examination, small entity. It is believed that no further fee is due with this response. However, if an additional fee is due, the Commissioner is herby authorized to charge the Deposit Account listed above referencing this case number.

CONCLUSIONS

In view of these amendments and remarks, the Applicants believe that the case is now in proper form for allowance. Prompt issuance of a Notice of Allowance is respectfully requested. If the Examiner believes that outstanding issues remain in the case, the Examiner is encouraged to call the undersigned Agent for Applicant listed below to discuss the matter.

Respectfully submitted,

Date: Feb 15, 2006

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